A Trial Simulation Example to Support the Design and Model-based Analysis of a New Dose and Regimen Finding Study

Didier Renard[1], Chyi-Hung Hsu[2], Michael Dolker[2], Vincent Yu[2], and Michael Looby[1]

[1]Modeling & Simulation, Novartis Pharma AG, Basel, Switzerland and

[2]Integrated Information Sciences, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Objectives

Use trial simulation as a general tool to make informed recommendations on the following aspects of a new dose and regimen finding study protocol:

- trial design, including the choice of a model-based vs. traditional analysis methods (Stage I),
  - sample size (Stage II),
  - analysis methodology (Stage III).

Methods

Trial simulations were performed in three stages.

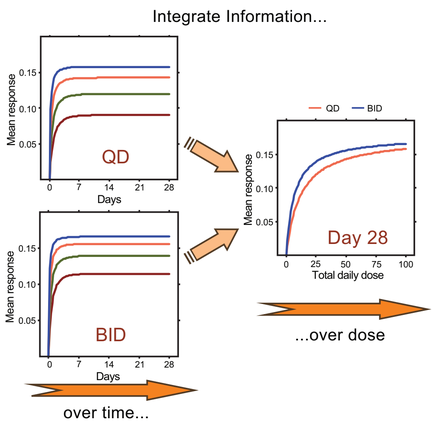
In Stage I the primary objective was to facilitate some trial design decisions. This included the choice of key design features such as parallel vs. crossover, dose levels, study visits, *etc.*, as well as the use of a model-based method vs. a traditional (ANCOVA) analysis method. The model-based approach evaluated at this stage was simplistic (same model for simulation and estimation purposes). Emphasis was on understanding the efficiency implications of the features under consideration. The median absolute deviation (MAD) from true value for quantities of interest (comparisons of active doses or placebo-corrected responses) was utilized as a measure to compare efficiencies of different design attributes.

In Stage II simulations were conducted to determine sample size based on the preferred design determined in Stage I.

Further simulations were conducted in Stage III to evaluate a more robust model-based analysis method which was articulated along 4 key principles:

1. Dose–response relationship is of E_{max} type.
2. Totality of data is included in the analysis, not just the end-point (see **Figure 1**).
3. Several candidate models, deemed a priori reasonable to describe the data, are considered.
4. Model averaging[1] is used to achieve more robust inference.

Figure 1. *Key principle in model-based analysis*



The models to describe the data assumed the dose–response component to be E_{max} or sigmoidal E_{max}, with regimen acting as a potency modifier and with common E_{max} across regimens. Those two assumptions support the use of an equivalent-dose approach for bridging once- and twice-daily regimens. Key differentiation was then in how each model describes the evolution of the response over time:

- **Steady state** (contrast first and later days):

$$E\{Y\} = E_0 + \frac{E_{max} \times \text{dose}^{\gamma}}{(ED_{50} \times \lambda^{I(\text{day}=1)} / \theta^{I(\text{BID})})^{\gamma} + \text{dose}^{\gamma}}$$

- **Longitudinal E_{max}** (characterization of time and dose dependencies through E_{max} type relationships):

$$E\{Y\} = E_0 + \frac{\text{day}}{ET_{50} + \text{day}} \times \frac{E_{max} \times \text{dose}^{\gamma}}{(ED_{50} / \theta^{I(\text{BID})})^{\gamma} + \text{dose}^{\gamma}}$$

- **Time-varying potency** (characterization of time dependency through E_{max} relationship on potency):

$$E\{Y\} = E_0 + \frac{E_{max} \times \text{dose}^{\gamma}}{(ED_{50} /(\frac{\text{day}}{ETP_{50} + \text{day}}) / \theta^{I(\text{BID})})^{\gamma} + \text{dose}^{\gamma}}$$

- **KPD** (assumption that dose enters the effect site in bolus with first-order elimination k):

$$E\{Y\} = E_0 + \frac{E_{max} \times \text{dose}^{\gamma}}{(ED_{50} /(\Theta^{I(\text{BID})} \times \exp(-k / 2^{I(\text{BID})}) \times (1 - \exp(-k \times \text{day})) /(1 - \exp(-k / 2^{I(\text{BID})}) / 2^{I(\text{BID})}))^{\gamma} + \text{dose}^{\gamma}}$$

While the sigmoidal E_{max} model offers more flexibility in dose–response shape, it is also more difficult to identify precisely parameters from such a model which makes it more prone to numerical issues. Having both versions, E_{max} and sigmoidal E_{max}, for each time–response model therefore helps balance risks and benefits associated with each of them. A total of 8 models [2 (dose–response) × 4 (time–response)] in the candidate set were thus considered. Random terms were included to represent inter-individual, inter-occasion (if applicable) and residual variability.

Model averaging, a formal method of accounting for model uncertainty among a series of competing models, was used to conduct more robust inference. For this purpose the Bayesian Information Criterion (BIC) was considered and BIC weights calculated as follows:

$$\frac{\exp(-0.5 \times BIC_m)}{\sum_{m'} \exp(-0.5 \times BIC_{m'})}.$$

Response predictions can be obtained as the weighted average of individual model predictions using BIC weights defined above. According to this formula models that best represent the data carry a greater weight in the prediction. Confidence limits around model-averaged predictions can be obtained using a parametric bootstrap procedure.

In Stage III, 10 simulation scenarios were set up: 8 of them based on models from the candidate set, one to test the effect of different E_{max} across regimens, and one representing slow attainment of pharmacodynamic steady-state through an exponential model to describe evolution over time. Simulations were performed to reflect current knowledge and uncertainty based on available clinical data. Measures such as bias, MAD, length and coverage of confidence intervals were used to contrast model-based and ANCOVA methods. Model-predicted quantities of interest were comparisons of active doses (*e.g.,* 50 q.d. – 25 b.i.d.) and placebo-adjusted responses at studied doses. The average across studied doses was also reported.

Results

Stage I: Simulations revealed that considerable improvements in precision can be expected from using the model-based approach over the traditional endpoint analysis. The choice of analysis method (model-based vs. ANCOVA) was the most discriminative feature amongst those investigated. Other design attributes such as parallel groups vs. crossover resulted in net efficiency gains one order of magnitude lower.

Stage II: Not further discussed here.

Stage III: Model averaging revealed good properties, with a favourable trade-off between bias (small in magnitude when present) and precision resulting in less variability overall (**Figure 2**). In particular, significant gains in efficiency remained over ANCOVA with greater benefits observed when comparing active doses (**Figure 2**). The procedure was slightly conservative when examining coverage probability (**Figure 3**).

Figure 2. *Median absolute deviation in predicted quantities of interest across Stage III simulations by scenario and modeling approach*

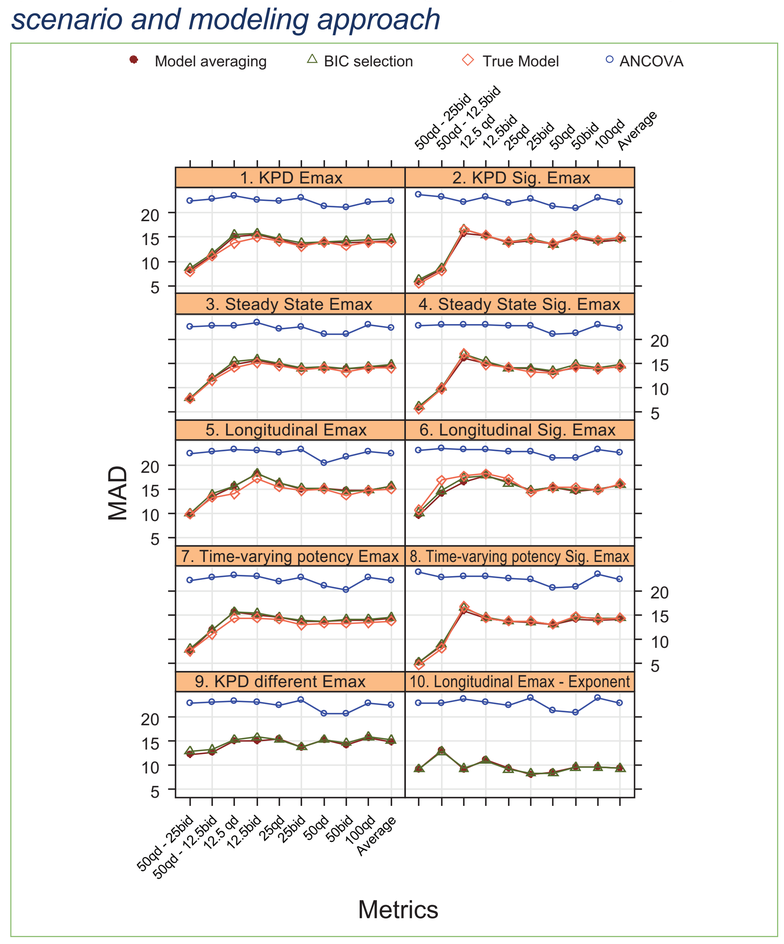
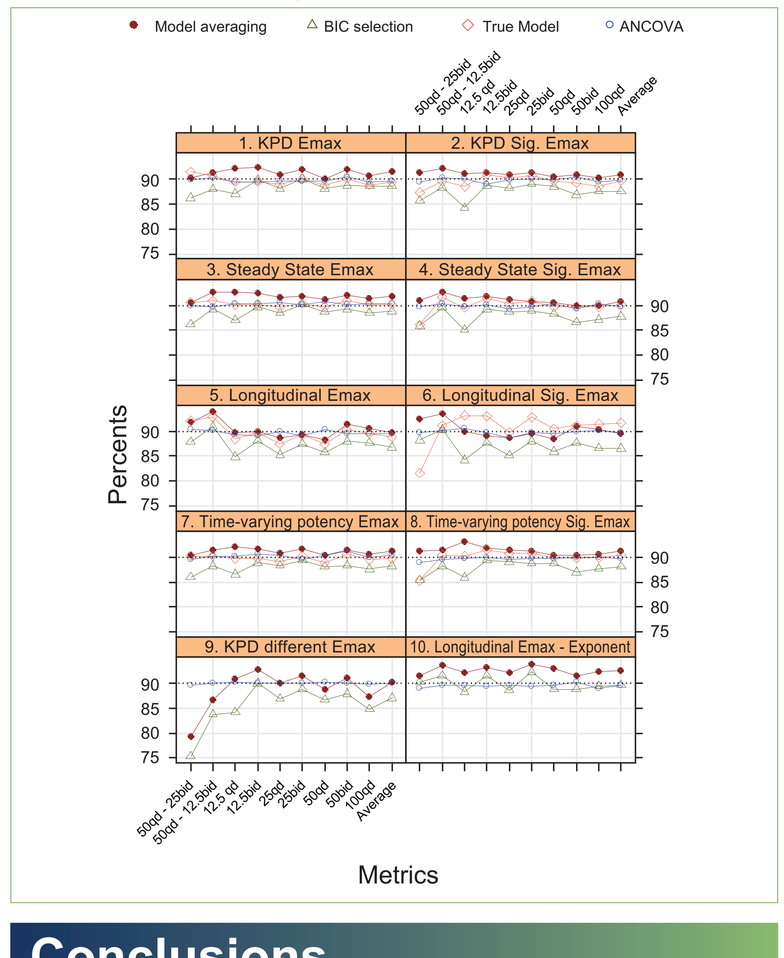


Figure 3. *Coverage probability of 90% CI for predicted quantities of interest across Stage III simulations by scenario and modeling approach*



Conclusions

Stage I and II of trial simulations allowed to determine key design features for the new study. The choice of a model-based method over ANCOVA was the primary factor to be considered to improve the overall study efficiency.

The proposed analysis methodology was shown to be robust and efficient, with a favourable trade-off between bias and precision, resulting in less variability overall. Greater benefits should be anticipated in comparisons of active doses rather than placebo-corrected responses, which is of particular importance when it comes to contrasting doses at the dose selection stage. The procedure was on the conservative side which should not be regarded negatively, at least within a regulatory context.

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Reference

1. Hoeting JA et al. *Stat Sci.* 1999;14:382–417.

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